

## **Consensus view on choice of iron chelation therapy in transfusional iron overload for inherited anaemias**

The goal of iron chelation therapy in multiply transfused patients is to prevent morbidity and early mortality from the toxic effects of transfusional iron overload, in particular cardiac deaths. At the same time treatment should be associated with as few drug-related side effects as possible. Desferrioxamine (Desferral), given parenterally, and the oral chelator, Deferiprone (Ferriprox), given as monotherapy or in combination are effective in clinical practice and have improved survival although both agents have disadvantages in routine use. A new oral drug, deferasirox (Exjade) has recently been licensed and clinical trial data suggests that it is effective at maintaining iron or achieving negative iron balance and its once-daily formulation may encourage adherence to treatment. Data on long term efficacy is not yet available. Thus clinicians and patients are faced with a choice of treatment. The following guidelines were based on consensus views of practising clinicians taking into account clinical experience and available clinical data and, as such, may change when new information becomes available.

### **General considerations**

- Consensus view is important to ensure consistency between patients and centres
- Decisions about chelation should be made by a consultant haematologist experienced in the use of chelation regimes
- The goal of chelation therapy is prevention rather than rescue; trends in ferritin levels need regular review with view to increasing dose or changing to an alternative drug(s).
- Management decisions should ideally be directed by results of ferritin levels and additional investigations (cardiac/liver iron estimation by T2\* MRI or liver R2 MRI or liver biopsy).
- T2\* estimations are feasible in older children and should routinely start from 10 yrs of age; below that will depend on clinical indications
- Patients need to be involved in decision making and information discussed with them should be backed up with written, impartial information. The principle of patient choice should be taken into account while making a clinical choice.
- If changed to a new medication, patients need to be aware of side effects and safety data. These patients will need reassessment at 3-6 months.
- Current evidence suggests that those with current or previous cardiac loading and/or cardiac problems should receive Deferiprone as part of their treatment unless this agent is not tolerated or not licensed for the age.
- Patients with acute cardiac decompensation e.g. cardiac failure or dysarrhythmias must receive IV Desferrioxamine (50 to 60mg/kg/day 24hrs with no breaks) to stabilise the heart. On recovery combination therapy should be considered.
- Efforts should be made to improve adherence to desferrioxamine (where used) by the use of disposable pre-filled infusors and suitable needles.

## Dosing guide

### *Desferrioxamine (DFO)*

- Licensed for all ages. Generally not started before the age of 2.
- Dose for children is 20-40 mg/kg/day (not above 30mg/kg/day in children age <5) Adult dose is 30- 50 mg/kg/day
- 5-6 infusions over 10-12 hours per week using an infusor pump. Disposable (Baxter) infusors are preferred.

Dose should be adjusted to therapeutic index to minimize toxicity. Note that this index is valid for thalassaemia patients only (see also below).

$$\text{Therapeutic index} = \frac{\text{Mean daily dose (mg/kg)}}{\text{Serum ferritin (}\mu\text{g/l)}} \quad \text{Maintain at } <0.025 \text{ at all times}$$

### *Deferiprone (DFP)*

- Not recommended for children age <6 (insufficient clinical information)
- Initial dose 25/mg/kg tds (better tolerated if started od and then built up over 4 weeks). Dose may be increased up to 100mg/kg/day.
- Agranulocytosis risk 1-2%. Monitor FBC weekly. Patients need to be continually educated about this risk, know that they must stop DFP if they have a fever or infection, and get a FBC done urgently. They should carry some written information explaining this

### *Deferasirox (DFX)*

- Licensed as second line agent for children age 2-5, and as first line agent in children age >5 and adults.
- Initial dose 20mg/kg/day. If iron stores are high, transfusion intensity >14ml/kg/month, or there is a trend of increasing iron stores with 20mg/kg/day, dose can be increased to 30mg/kg/day.
- Serum creatinine should be tested in duplicate before commencing therapy, and renal function estimated by creatinine clearance. Serum creatinine, liver enzymes and urine protein on dipstix should be monitored weekly for the first month, then monthly. Dosage reduction (by 10 mg/kg/day) or discontinuation is necessary if there is a trend of increasing creatinine. Measure serum ferritin 3 monthly.

### **Combination therapy**

- Desferrioxamine, as above, 2-6 infusions/week **plus** Deferiprone, as above, 7 days/week
- This is not a life-long treatment and is intended as intensive chelation to reduce iron stores rapidly and reliably
- There is no experience of Desferrioxamine in combination with Deferasirox and this treatment is NOT recommended
- Risks of agranulocytosis and desferrioxamine toxicity are probably increased with combination therapy, and this treatment needs more intensive monitoring, including regular weekly blood counts, 3 monthly biochemistry, ferritin and zinc levels, 6 monthly T2\* MRI and audiometry.
- Desferrioxamine frequency should be decreased as ferritin level falls. Patients with consistent ferritin levels below 1000 could be considered for deferiprone monotherapy

### **Monitoring**

All patients on iron chelation require careful monitoring:

- Monthly biochemistry (creatinine and liver function tests)
- 3 monthly clinic visit and serum ferritin
- Annual audiometry and ophthalmology
- T2\*MRI (>10yrs)
- Additionally, patients on Deferiprone require careful monitoring of neutrophil counts (preferably weekly), education about the risk of agranulocytosis and a letter to present to A&E if unwell with fever.

Ferritin levels may be inconsistent, particularly in sickle cell patients, and decisions should not be based on individual results but trends over time.

## CONSENSUS GUIDELINES

### Key:

DFO = Desferrioxamine

DFP = Deferiprone

DFX = Deferasirox

Definition of not tolerated:

- local or systemic side effects limiting ability to use appropriate dose of desferrioxamine and/or Deferiprone
- patients unable to adhere to desferrioxamine despite education and measures to improve compliance e.g. pre-filled infusors

### THALASSAEMIA

#### 1. Previously untreated patients

Discuss options and available data with patients/parents.

##### a) Children age 2-5:

1<sup>st</sup> line: DFO 20-40 mg/kg 5-6 nights per week over 10-12 hours

2<sup>nd</sup> line: DFX 20-30 mg/kg/day

##### b) Children age > 5:

1<sup>st</sup> line: DFX 20-30 mg/kg/day

2<sup>nd</sup> line: DFO 20-40 mg/kg 5-6 nights per week

#### 2. Patients at increased risk of cardiac disease:

- LV impairment (low ejection fraction, dilated LV on ECHO, MUGA or MRI)
- Changing ECG patterns, in particular development of RV strain
- Cardiac loading on T2\* MRI (T2\* < 15ms)

1st line: Chelation should incorporate DFP either as part of combination or as monotherapy

2<sup>nd</sup> line: Change to DFX if above regimen not tolerated. If neutropenia on DFP consider i.v DFO if low LVEF

The choice of chelator should be reviewed when cardiac function and T2\* return to normal and will depend on hepatic iron stores, patient tolerance and ferritin levels (see below). Deferiprone monotherapy is an option for those with satisfactory iron stores.

#### 3. Acute cardiac decompensation:

These patients require intensive chelation: treat with continuous i.v DFO over 24 hr at 50 mg/kg/day via port-a-cath. After 1-2 weeks, DFP may be introduced.

#### 4. Other patients

The choice of chelation for patients not falling into the above categories should be the result of a decision taken between the patient and an experienced clinician taking into account:

- Tolerance of current treatment
- Current iron stores as evidenced by serum ferritin levels and liver/heart imaging techniques
- Trends in ferritin levels
- Patient choice

The current state of knowledge on the efficacy and toxicity **all** chelating drugs should be presented in a clear form to patients whatever their current drug regimen.

The choice of chelator regimen and doses should be reviewed at 6-12 month intervals.

##### *Choice of chelating regimen:*

##### **a) Patients with satisfactory iron stores:**

- Serum ferritin consistently 750-1500 mcg/l
- Liver iron (if available) <7mg/g dry weight- by T2\* MRI, R2 MRI or direct quantitation from liver biopsy
- Cardiac T2\* MRI >15 m sec (if <15ms, treat as high risk for cardiac disease – see above)

1. Continue current regimen and offer means to improve ease of treatment (e.g disposable pumps), if applicable
2. Offer DFX if patient requests change after full discussion or if current regimen not tolerated

##### **b) Patients with high iron stores**

- Serum ferritin consistently > 1500 mcg/l or increasing trend  
and/or
- Liver iron >7 mg/g dry weight- by T2\* MRI, R2 MRI or direct quantitation from liver biopsy
- Cardiac T2\* MRI >15 m sec (if <15ms, treat as high risk for cardiac disease – see above)

1. Increase doses of current chelation drugs to maximum dose as tolerated and adjusted to therapeutic index
2. If on DFP monotherapy change to DFO
3. Explore adherence issues; offer disposable pre-filled infusors if not already using these
4. Change to DFX if patient unable to increase chelation or not tolerant of DFO

#### 5. Patients for whom T2\* results not available

##### **a) Abnormal ECG and/or ECHO and/or clinical cardiac history thought to be related to cardiac iron deposition**

- 1st line: Chelation should incorporate DFP either as part of combination or as monotherapy
- 2<sup>nd</sup> line: Change to DFX if above regimen not tolerated

##### **b) Normal ECHO/ECG and no cardiac history**

Individual decision based on ferritin trends and tolerance of treatment as detailed above.

## **SICKLE CELL DISEASE, OTHER TRANSFUSION DEPENDENT ANAEMIAS**

### **1. Previously untreated patients**

Discuss options and available data with patients/parents.

- 1<sup>st</sup> line: DFO 20-40 mg/kg 5-6 nights per week over 10-12 hours
- 2<sup>nd</sup> line: DFX 20-30 mg/kg/day

### **2. Other patients/ patients already on treatment:**

The choice of chelation for these patients should be the result of a decision taken between the patient and an experienced clinician taking into account:

- Tolerance of current treatment
- Current iron stores as evidenced by serum ferritin levels and liver/heart imaging techniques
- Trends in ferritin levels
- Patient choice

The current state of knowledge on the efficacy and toxicity **all** chelating drugs should be presented in a clear form to patients whatever their current drug regimen.

The choice of chelator regimen and doses should be reviewed at 6-12 month intervals.

**Choice of chelating regimen:** Chelation with DFO or DFX is recommended for treatment. See thalassaemia section above.

*Additional notes:*

*Sickle Cell*

- DFX has been compared to DFO in a phase III study of children and adults with sickle and appears to be safe and equally efficacious
- Ferritin levels may be unreliable in sickle cell patients; therefore the use of the therapeutic index is less helpful in this group. The trend in ferritin level may be a useful indicator of iron stores and chelation efficacy. In general, these patients should also be monitored with T2\*MRI and R2 MRI
- Clinical evidence suggests that Sickle cell patients are less likely to have cardiac iron deposition.
- There is very little data on use of DFP in sickle cell. DFP monotherapy may be considered in individual circumstances at the discretion of the haematologist.
- Renal impairment is relatively common in adults with sickle cell, and the serum creatinine is not a sensitive marker. There have been cases of renal failure in patients with SS on DFX. This is expected to be a particular risk during a severe vaso-occlusive crisis or other sickle-related complication. Monitoring of renal function, avoidance of other nephrotoxic drugs and maintenance of adequate hydration is especially important for these patients

*Other anaemias*

- 1. The risk of agranulocytosis and other cytopenias with DFP appears to be increased in patients with Diamond Blackfan anaemia.
- DFP should not be used in patients with bone marrow disorders (Diamond Blackfan, Aplastic anaemia, PNH, MDS)
- DFX has specifically been studied in adults and children with rare transfusion dependent anaemias and would be a suitable alternative to DFO

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**GUIDELINES FOR CHOICE OF IRON CHELATOR IN TRANSFUSION-DEPENDENT PATIENTS WITH INHERITED ANAEMIAS**

<b>Patients</b>	<b>Average serum Ferritin (µg/L)</b>	<b>Cardiac loading (MRI)*</b>	<b>Hepatic loading (MRI)*</b>	<b>Treatment Options</b> DFO = Deferrioxamine (s/c) DFP = Deferriprone (oral) DFX = Deferasirox (oral)
<b>Previously unchelated patients 2-5y</b>				1. DFO 2. DFX if DFO refused, not tolerated or inadequate
<b>Previously unchelated patients &gt;5y</b>				1. DFX 2. DFO if DFX not tolerated or inadequate
<b>Patients intolerant of DFO</b>	Any	Any	Any	1. DFX
<b>Previously chelated patients</b>	< 1500µg/L	0	<7mg/kg/dw	1. Continue current regimen 2. DFX, if patient requests
	< 1500µg/L	0	>7mg/kg/dw	1. Increase dose of DFO (consider use of pre – filled syringes) 2. If on DFP monotherapy change to DFO 3. DFX if DFO not tolerated or unsuccessful
	Any	T2* < 15 ms or abnormal cardiac function on ECHO	Any	1. DFP +/- DFO; push doses and adherence (consider use of pre – filled syringes) 2. DFX if not tolerated or unsuccessful
	> 1500µg/L	0	Any	1. DFO at increased doses, if tolerated (consider use of pre – filled syringes) 2. DFX if not tolerated or unsuccessful

<b>T2* not available</b>	Any	clinical symptoms, abnormal cardiac function on ECHO, changing ECG	Any	<ol style="list-style-type: none"> <li>1. DFO+/- DFP; push doses and compliance (consider use of pre – filled syringes)</li> <li>2. DFX if not tolerated or unsuccessful</li> </ol>
	Any	Normal ECG/ ECHO no history	Any	Individual decision based on ferritin adherence and patient choice.



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